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Reviews

Caffeine physical dependence: a review of human and laboratory animal studies

Roland R. Griffiths[1, 2] and Phillip P. Woodson[1]

[1] Department of Psychiatry and Behavioral Sciences and [2] Department of Neuroscience, The Johns Hopkins University School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205, USA

Abstract. Although caffeine is the most widely used behaviorally active drug in the world, caffeine physical dependence has been poorly characterized in laboratory animals and only moderately well characterized in humans. In humans, a review of 37 clinical reports and experimental studies dating back to 1833 shows that headache and fatigue are the most frequent withdrawal symptoms, with a wide variety of other signs and symptoms occurring at lower frequency (e.g. anxiety, impaired psychomotor performance, nausea/vomiting and craving). When caffeine withdrawal occurs, severity can vary from mild to extreme (i.e. incapacitating). The withdrawal syndrome has an onset at 12–24 h, peak at 20–48 h, and duration of about 1 week. The pharmacological specificity of caffeine withdrawal has been established. The proportion of heavy caffeine users who will experience withdrawal symptoms has been estimated from experimental studies to range from 25% to 100%. Withdrawal symptoms have been documented after relatively short-term exposure to high doses of caffeine (i.e. 6–15 days of ≥600 mg/day). Although animal and human studies suggest that physical dependence may potentiate the reinforcing effects of caffeine, human studies also demonstrate that a history of substantial caffeine intake is not a necessary condition for caffeine to function as a reinforcer. The similarities and differences between caffeine and classic drugs of abuse are discussed.

Key words: Caffeine – Caffeinism – Coffee – Tea – Physical dependence – Withdrawal – Reinforcer – Drug self-administration – Subjective effects – Drug dependence – Drug abuse – Humans – Animals

Introduction

Caffeine is the most widely used behaviorally active drug in the world (Gilbert 1984), with 82–92% of adults in North America regularly consuming caffeine (Gilbert 1976a; Graham 1978). Presently, worldwide per capita caffeine consumption has been estimated to be 70 mg per day which is the equivalent of a large cup of instant coffee or a small cup of ground coffee for every man, woman and child (Gilbert 1984; Barone and Roberts 1984). In the United States and Canada, daily per capita caffeine consumption has been estimated to be 211 and 238 mg, respectively. These figures are about half those estimated for the United Kingdom (444 mg) and Sweden (425 mg), which are particularly heavy tea and coffee consuming countries, respectively (Gilbert 1984).

After oral administration to humans, caffeine is rapidly and completely absorbed, reaching maximal plasma levels at about 30 min (Blanchard and Sawers 1983). The principal pharmacological actions of acute caffeine administration are to stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle, decrease peripheral vascular resistance while increasing cerebrovascular resistance, increase gastric and other secretions, and relax smooth muscle, most notably bronchial muscle (Rall 1985; Bättig 1985). With repeated or chronic administration, tolerance occurs to various behavioral and physiological actions of caffeine (Hirsh 1984; Finn and Holtzman 1986). Caffeine is principally eliminated by metabolism in the liver and has an average plasma half-life of about 3–6 h in humans (Kalow 1985).

The chronic use of a tolerance-inducing drug which has a moderate to rapid elimination rate makes that compound a good candidate for producing physical dependence as manifested by biochemical, physiological or behavioral disruptions occurring upon termination of drug administration. Although clinically significant caffeine physical dependence has been periodically described in medical reports dating back at least over the last century and a half, caffeine physical dependence is not widely recognized by the lay population or by health-care professionals. For example, the most recent version of the influential diagnostic manual of the American Psychiatric Association (DSM-III-R) does not acknowledge the existence of caffeine physical dependence (American Psychiatric Association 1987).

The purpose of this paper is to review and evaluate the current scientific understanding of the physical dependence producing effects of caffeine. Sections II and III review studies documenting caffeine physical dependence in laboratory animals and humans, respectively. The subsequent section (Section IV) reviews human studies suggesting that physical dependence may be an important determinant of the reinforcing effects of caffeine. Section V discusses pharmacological and physiological mechanisms of caffeine physical dependence, while the final section (Section VI) considers the controversial question of whether caffeine can meaningfully be considered to be a drug of abuse.

Physical dependence in laboratory animals

Although methods have been well established for evaluating the physical dependence potential of various drug classes in laboratory animals (Martin 1977; Brady and Lukas

Offprint requests to: R.R. Griffiths

1984), surprisingly few studies have been conducted with caffeine. Six reports have been published using rats, most of which document substantial behavioral disruptions following cessation of chronic caffeine dosing (Boyd et al. 1965; Vitiello and Woods 1977; Carney 1982; Holtzman 1983; Finn and Holtzman 1986; Holtzman and Finn 1987).

The most reliable caffeine withdrawal effect has been decreased locomotor activity. Boyd and colleagues (1965) reported that termination of drug treatment (100 days of 190 mg/kg/day caffeine intragastrically for 5 days a week) was followed by a decrease in locomotor activity to half that before withdrawal and half that in nondrugged control animals. The decreased locomotor activity lasted 1 week, and was accompanied by a slight but significant decrease in colonic temperature and an increase in urinary protein and glucose. Holtzman showed that decreased locomotor activity during caffeine withdrawal is dose dependent. Groups of rats which drank an average of 19 or 36 mg/kg/day caffeine for 6 weeks showed no change in locomotor activity, whereas animals consuming 67 mg/kg/day showed decreased locomotor activity following substitution of water for caffeine (Finn and Holtzman 1986). This decrease lasted 2 days and was maximal on the 1st day of withdrawal (about 50% of pre-withdrawal levels). In a similar experiment by Holtzman (1983), decreased locomotor activity was shown following substitution of water for caffeine (11 weeks of exposure to caffeine; approximately 160 mg/kg/day during the last 7 weeks). This decrease lasted 4 days and was maximal on the 2nd day of withdrawal (about 80% of prewithdrawal levels).

Disruption of operant schedule-controlled behavior during caffeine withdrawal has been less reliably demonstrated than the decreased locomotor activity. Carney (1982) showed a 50% decrease in food-maintained lever pressing behavior on days when rats were injected intraperitoneally with saline rather than a standard daily dose of 32 mg/kg caffeine. Another study (Holtzman and Finn 1987), however, failed to show disruption of lever pressing in rats during caffeine withdrawal (50 and 90 mg/kg/day for 1 month).

The only other preclinical study to provide information about caffeine withdrawal was one which used a taste-aversion paradigm to provide evidence for both the aversive properties of caffeine in naive rats and the aversive properties of absence of caffeine in rats repeatedly exposed to caffeine (Vitiello and Woods 1977). In this study injections of caffeine to naive rats produced a dose-related avoidance of a novel flavor associated with caffeine. However, rats which had previously received injections of caffeine on each of 12 days (approximately 1.5–12 mg/kg/day) showed a dose-related avoidance of a novel flavor associated with the absence of caffeine.

In contrast to the numerous reports and studies of caffeine withdrawal in humans to be reviewed in Section III, the relatively few reports investigating the effects of caffeine withdrawal in laboratory animals is striking, particularly given the established utility of such animal models for characterizing physical dependence and pharmacological mechanisms of action of various drug classes (Martin 1977; Brady and Lukas 1984). The only reliable behavioral effect of caffeine withdrawal to have been clearly documented in laboratory animals is decreased locomotor activity in rats. Parametric studies are needed to define the behavioral and species generality of these caffeine withdrawal effects. Given the relatively subtle nature of the observable behavioral effects of caffeine withdrawal in humans, it should be anticipated that characterization of analogous effects in laboratory animals may prove to be an experimental challenge.

Physical dependence in humans

As in research with laboratory animals, experimental methods have been established for evaluating the physical dependence potential of drugs in humans (Martin 1977; Brady and Lukas 1984; Petursson and Lader 1984). Caffeine physical dependence, as revealed by a withdrawal syndrome following cessation of chronic caffeine dosing, has been clearly and repeatedly documented. Tables 1 and 2 summarize 37 reports, including case reports, clinical observations, experimental studies and survey studies, which provide information about the signs, symptoms and time course of the caffeine withdrawal syndrome.

In assembling the tables, 25 published reports which may have some relevance to caffeine dependence were purposely excluded. Twelve reports of abrupt and/or gradual withdrawal from caffeine after chronic, high dose caffeine consumption were excluded from the tables because it was unclear whether caffeine withdrawal signs or symptoms were explicitly looked for or documented (Roch 1914; Ross 1971; Greden 1974, case # 2; Molde 1975; De Freitas and Schwartz 1979; Foxx and Rubinoff 1979; Hyner 1979; Bernard et al. 1981; Young et al. 1982; Khoury and Maltbie 1984; James et al. 1985, 1987). Eleven reports describing various withdrawal signs and symptoms occurring upon abstinence after long-term use of products containing caffeine in combination with other pharmacologically active compounds (e.g. aspirin, phenacetin, antipyrine, oxycodone) were excluded from the tables because the results cannot be attributed solely to caffeine (Schilling 1928; Idestrom 1960; Miller 1960; De Busscher and Varenne 1966; Gault et al. 1968; Kielholz 1970; Murray 1973; Burns 1977; Gardos 1977; Babington and Monson 1982; Granella et al. 1987). Two reports were also excluded which described withdrawal signs and symptoms after long-term use of combination products containing theophylline, an analog of caffeine (Laux 1979; Horowitz et al. 1982). Although a report by Vojtěchovský and Šafratová (1972) was cited in a prominent review paper as providing a possible example of caffeine withdrawal headache (Gilbert 1976a), this report was excluded from the tables because it is not clear that the study involved a meaningful duration of caffeine abstinence.

Signs and symptoms of caffeine withdrawal. Tables 1 and 2 show that headache is the most frequently reported withdrawal symptom (19 reports). Possibly related, two additional case reports described "fullness" in head and pressure in head or facial flushing, but no headache as part of the withdrawal syndrome (Cobbs 1982; Wilkin 1986). Caffeine withdrawal headache has been characterized as being gradual in development (Dreisbach and Pfeiffer 1943; Greden et al. 1980; Roller 1981), diffuse (Dreisbach and Pfeiffer 1943; Greden 1974; Greden et al. 1980), throbbing (Dreisbach and Pfeiffer 1943; Greden 1974; Greden et al. 1980), severe (Bridge 1893; Dreisbach and Pfeiffer 1943; Naismith et al. 1970; Greden 1974; Greden et al. 1980; Weil and Rosen 1983 p 183; Rainey 1985), and phenomeno-

Table 1. Summary of case reports and clinical observations relevant to caffeine withdrawal in humans

Reference	Subjects	Type of report and history of caffeine use	Withdrawal signs and symptoms
Kingdon (1833)	$N=1$	Case report; description of effects of abstaining from morning tea	Always experienced mental confusion which was relieved by tea
Guelliot (1885a)	$N=2$ [Cases # 3 & 6]	Case reports; two patients (3–12 cups of coffee/day) with signs and symptoms of caffeinism, abstained from coffee	Concurrent medical problems and insufficient detail make these case reports difficult to interpret; upon complete or partial abstinence from coffee, both patients experienced insomnia which was apparently suppressed by coffee consumption
	$N=1$ [Case # 5]	Case report; patient was a heavy habitual coffee user; description of effects of overnight abstinence	Psychomotor impairment due to marked limb tremor occurred after overnight abstinence and was apparently suppressed by coffee consumption
Mendel (1889)		Clinical observations; patients who were heavy habitual coffee users abstained from coffee	Weakness and dysphoria occur during the first weeks of coffee cessation; protracted withdrawal signs or symptoms may occur for several months
Bridge (1893)		Clinical observations; patients who were habitual coffee users abstained from coffee	In susceptible individuals, severe incapacitating headaches described as occurring during first day or two after abrupt coffee abstinence; constipation described as occurring occasionally
Gilles de la Tourette and Gasne (1895)	$N=1$ [Case # 2]	Case report; patient was a heavy habitual coffee user; description of effects of overnight abstinence	Marked hand tremor after overnight abstinence was partially suppressed after first cup of coffee in the morning
Stransky (1932)	$N=1$	Case report; patient who had been eating up to and over 5 handfuls of roasted coffee beans and consuming several cups of coffee daily for 2 yrs abstained from consuming coffee beans	Patient became tired and sleepy
	$N=1$	Case report (first-person account); heavy user of caffeinated beverages; description of symptoms of intermittent abstinence	Abstinence from caffeinated beverages associated with a mild irritability/uneasiness combined with tiredness, sleepiness (yawning), and impairment in work- and thought-related activities
Wagner (1939)	$N=1$	Case report; patient who consumed coffee prepared from 250 to 375 g of ground coffee daily abstained from coffee when hospitalized with a variety of medical problems	Delirium described as a possible withdrawal sign
Franklin et al. (1948)	$N=36$	Clinical observations; during a semi-starvation experiment with male subjects, large amounts of coffee or tea (limited to a maximum of 9 cups/day) were consumed; subjects were occasionally exposed to 3-day periods of greatly reduced fluid intake	Although not explicitly evaluated, a few subjects complained of headache and increased lassitude during periods of restricted caffeine and fluid intake
In Der Beeck (1961)	$N=1$	Case report; patient was a heavy coffee drinker (coffee prepared from at least 100 g of ground coffee each day); description of symptoms of coffee abstinence	Feelings of apathy, lethargy, listlessness during coffee abstinence were suppressed by coffee consumption
Reimann (1967)	$N=1$	Case report; patient consumed an estimated 1.5–1.8 g caffeine/day in coffee; coffee intake was restricted to one cup/day	None
Greden (1974)	$N=1$ [Case # 1]	Case report; patient who was a heavy coffee drinker (10–12 cups/day over last three weeks) abstained from coffee	Fatigue was reported for 1 wk after coffee abstinence
	$N=1$ [Case # 3]	Case report; patient consumed caffeine-containing beverages and analgesics (estimated 1.5 g caffeine/day); description of symptoms apparently correlated with reduced caffeine intake	Severe headache; relief of headache obtained with analgesics containing caffeine but not with caffeine-free analgesics
Shorofsky and Lamm (1977)		Clinical observation; heavy coffee users; description of symptoms during short-term (24-h) religious fasts	Withdrawal headache described as a common problem

Table 1. (continued)

Reference	Subjects	Type of report and history of caffeine use	Withdrawal signs and symptoms
Greden et al. (1980)	$N=1$	Case report; patient who was a heavy caffeine consumer (greater than 500 mg caffeine/day over 20 years) sharply reduced or eliminated caffeine intake	Headache began 18–20 h after abstinence, peaking 3 h after onset and lasting at least 36 h unless caffeine consumed; accompanied by rhinorrhea, fatigue, yawning; patient reported being able to smell coffee, even when none was present; headache was suppressed by coffee consumption
Gibson (1981)	$N=1$	Case report; depressed patient was a heavy coffee drinker (10–15 cups/day); description of effects of abrupt caffeine abstinence upon admission to a metabolic ward	On 2nd and 3rd day of caffeine abstinence urinary MHPG increased along with anxiety and headache
Cobbs (1982)	$N=1$	Case report; diabetic patient consumed up to 30 cups of coffee/day; description of symptoms of intermittent coffee abstinence	Periods of coffee abstinence associated with "fullness" and pressure in head (onset 3–5 h), "let-down" (onset 4–6 h), lethargy, fine motor impairment, confusion; other possible symptoms included muscle stiffness, blurred vision, slowed speech, diaphoresis, and anxiety attacks; withdrawal symptoms apparently suppressed by coffee consumption
Weil and Rosen (1983 p 183)	$N=2$	Case report (first-person account); two heavy habitual coffee users switched to decaffeinated coffee	Severe headache (both individuals) and tiredness (one individual) occurred on 2nd day after switching to decaffeinated coffee; symptoms were suppressed by caffeinated coffee consumption
Rainey (1985)	$N=1$	Case report; patient consumed an estimated 834 mg caffeine/day in caffeine-containing beverages and analgesic tablets; treatment consisted of abstinence from all methylxanthines	Headache, irritability, nervousness, vomiting, insomnia, restlessness, and lethargy were reported over a 3-day period.
Wilkin (1986)	$N=1$	Case report; patient consumed 8–12 cups of coffee/day excepting weekends when 1 cup/day was consumed	Weekend syndrome of facial reddening accompanied by "blood shot" eyes and sensations of "fullness" and warmth; symptom onset late Saturday morning and most intense on Saturday evening

logically distinct from migraine headache (Dreisbach and Pfeiffer 1943). Although headache is the most frequently reported withdrawal symptom, it should be noted that several clinical reports have concluded that acute caffeine (Marburg 1899; Hollingworth 1912; Dreisbach and Pfeiffer 1943) or coffee (Guelliot 1887; Schulte 1950; Harrie 1970) administration can *induce* headache in some individuals.

In addition to headache, a constellation of symptoms frequently reported during caffeine withdrawal is characterized by fatigue (i.e. mental depression, let-down, fatigue, weakness, lethargy, lassitude, apathy, listlessness, tiredness, sleepiness, drowsiness, yawning, disinclination to work, lazy, and decreased activeness and alertness). Tables 1 and 2 show that 15 separate reports described such symptoms.

A third possible dimension of the caffeine withdrawal syndrome is anxiousness (i.e. anxious, nervous, jittery, shaky, muscle tension, restless, and insomnia). Although this dimension has been described in eight reports in Tables 1 and 2, the supporting evidence is not as compelling as that for headache and fatigue (Goldstein et al. 1969; Griffiths et al. 1986a).

A wide variety of other signs and symptoms have been reported to occur during caffeine withdrawal, but at a relatively low frequency. These signs and symptoms, with the number of reports from the tables indicated in parentheses, include impaired psychomotor preformance and/or marked limb tremor (5), irritability/uneasiness (4), rhinorrhea (3), nausea/vomiting (2), confusion (2), diaphoresis (2), muscle pains/stiffness (2), inability to work effectively (2), decreased contentedness (1), dysphoria (1), blurred vision (1), slowed speech (1), constipation (1), scleral injection (1), facial warmth (1), delirium (1), olfactory hallucination (1), decreased cigarette smoking (1), increased cerebral blood flow (1), increased urinary MHPG (1), decreased lymphocyte β-adrenoceptor sensitivity (1), lowered serum calcium (1), and elevated serum phosphorus (1). "Craving" for coffee has also been described, although not empirically documented, as a coffee withdrawal symptom (Goldstein et al. 1974; Rippere 1984). For the most part, these miscellaneous signs and symptoms have not been rigorously evaluated in experimental studies and thus their reliability as part of the caffeine withdrawal syndrome remains to be established.

Severity. When signs or symptoms of caffeine withdrawal occur, the severity can vary from mild to extreme. At its worst, caffeine withdrawal has been repeatedly documented to be incompatible with normal functioning and sometimes totally incapacitating (Kingdon 1833; Bridge 1893; Dreisback and Pfeiffer 1943; Goldstein and Kaizer 1969; Greden

Table 2. Summary of experimental and survey studies relevant to caffeine withdrawal in humans

Reference	Subjects	Design	Withdrawal signs and symptoms
Horst et al. (1934)	$N = 7$ adult men	Withdrawal not blind; after receiving caffeinated coffee (estimated 3–4 mg/kg caffeine) once daily for 1–8 wks, coffee dosing was abruptly terminated	Results of this non-blind study are difficult to interpret; some suggestive evidence for impaired psychomotor performance during 1st wk of withdrawal
Dreisbach and Pfeiffer (1943)	$N = 22$ mostly men; graduate and medical students	Single-blind; caffeine administered in capsules in increasing doses over 6–7 days to 600–750 mg/day; placebo capsules substituted for caffeine capsules	Lethargy in morning, cerebral fullness at noon, and headache in early afternoon, reaching peak intensity 3–6 h later; nausea, vomiting, rhinorrhea, lowered serum calcium and elevated serum phosphorus accompanied headache in some subjects; other withdrawal symptoms included mental depression, drowsiness, yawning, and disinclination to work; withdrawal headache was suppressed by caffeine; 82% of the subjects reported definite or severe withdrawal headache while the remaining subjects reported very slight or no headache
Goldstein (1964)	N = approximately 109 [Experiments c and d] mostly men; medical students	Double-blind; subjects abstained from caffeine after lunch and received 150 mg caffeine or placebo in decaffeinated coffee at bedtime over 4 successive nights with both treatments being given twice	In subjects with histories of heavy coffee use (5 or more cups/day), morning headache occurred significantly more frequently after placebo (25% of trials) than after caffeine (3% of trials); among moderate coffee users (2–4 cups/day) the frequency of headache was nonsignificantly higher after placebo (12% of trials) than after caffeine (7% of trials); in light coffee users (0 or 1 cups/day) the frequency of headache was equally low after placebo and caffeine
Goldstein and Kaizer (1969)	$N = 183$ wives of graduate students	Questionnaire survey (no experimental manipulation); consequences of omission of morning coffee	Moderate (3–4 cups/day) and especially heavy coffee users (5–10 cups/day) reported irritability, inability to work effectively, nervousness, restlessness, lethargy, headache; light coffee users (1–2 cups/day) did not report these symptoms; percentages of light, moderate and heavy coffee users reporting headache were 0, 9, and 8%, respectively
Goldstein et al. (1969)	$N = 56$ wives of graduate students	Double-blind; subjects abstained from caffeine after dinner and received placebo, 150 mg or 300 mg caffeine (free base) in decaffeinated coffee the following morning (about 9 A.M.); this procedure occurred repeatedly over a 9-day period with each treatment being given 3 times	Compared to subjects who were not regular coffee drinkers, heavy coffee users (5 or more cups/day) reported being less alert, active and content, and more sleepy, irritable, and jittery/nervous/shaky after caffeine abstinence; caffeine generally produced a dose-related suppression of withdrawal symptoms (including headache) in the heavy users
Naismith et al. (1970)	$N = 20$ male and female staff from a department of nutrition	Not blind; after a 10-day baseline period (estimated dietary caffeine intake of 560 mg/day) subjects switched abruptly to decaffeinated coffee	All subjects reported lassitude and severe headache within 12 h of caffeine abstinence; symptoms disappeared after a further 36 h
Winstead (1976)	$N = 135$ mostly adult men; inpatients on an acute psychiatric ward	Questionnarie survey (no experimental manipulation) of occurrence of coffee withdrawal symptoms; 25% of the group were defined as heavy coffee users (i.e. estimated to consume at least 500 mg/day on at least 2 study days)	Anxiety withdrawal symptoms were reported more frequently by the heavy user group (26%) than by other patients (5%)
Greden et al. (1978)	$N = 83$ mostly men; adult psychiatric inpatients	Questionnaire survey (no experimental manipulation) of occurrence of headache on omission of morning caffeine	11% reported headache; no significant differences between light, moderate or heavy caffeine users
Greden et al. (1980)	$N = 205$ hospitalized patients	Questionnaire survey (no experimental manipulation) of occurrence of headache upon stopping routine caffeine consumption	20% of total sample (28% of the 152 who answered the question) reported caffeine withdrawal headache; those reporting headache had higher mean caffeine intake (616 mg/day) than those not reporting headache (395 mg/day)

Table 2. (continued)

Reference	Subjects	Design	Withdrawal signs and symptoms
White et al. (1980)	$N = 36$ college students	Double-blind; subjects abstained from caffeine for at least 3 hrs; muscle tension was measured with electromyogram before and 30 min after either 300 mg caffeine citrate ($N = 19$) or placebo ($N = 17$); anxiety and reaction time assessed after drug or placebo administration	Before caffeine or placebo, high caffeine consumers (376 mg over previous 24 h) showed more muscle tension than did low consumers (87 mg over previous 24 h); among subjects receiving placebo, anxiety was positively correlated with level of prior caffeine consumption
Mackenzie et al. (1981)	$N = 7$ adult men	Not blind; subjects abstained from caffeine after at least 3 months of daily coffee drinking with estimated caffeine intake of 400 mg/day	On day 3 of caffeine abstinence a decrease in lymphocyte beta-adrenoceptor sensitivity occurred in all subjects; by day 7 some sensitivity was regained in 5 of 7 subjects
Robertson et al. (1981)	$N = 18$ adult men and women	Double-blind; caffeinated barley-based beverage served 3 times/day (750 mg caffeine/day) for 7 days followed by substitution of a placebo barley-based beverage	Despite nearly complete tolerance to caffeine's effects on several humoral and hemodynamic variables, substitution of placebo did not result in any detectable effects on these measures
Roller (1981)	$N = 1$ adult man	A heavy coffee drinker (900–1100 mg caffeine/day) abstained from caffeine for a 72-h period; theophylline was given at 24 h into this 72 h period; at the end of 72 h either caffeinated coffee (approx 115 mg caffeine) or decaffeinated coffee was given in a blinded fashion; this protocol was replicated on 9 occasions	Withdrawal symptoms started after about 6 hrs with headache; shortly thereafter came lassitude, then rhinorrhea and leg muscle pains, followed by diaphoresis; after 16 h of abstinence came general muscle pains (flu-like symptoms); these symptoms gradually increased to a maximum intensity at a later time and were suppressed by caffeinated coffee consumption
Victor et al. (1981)	$N = 124$ male and female medical inpatients	Questionnaire survey (no experimental manipulation) of occurrence of caffeine withdrawal headache	24% of all subjects reported withdrawal headache; differences between low, moderate, and high caffeine consumers were apparently not significant
Ammon et al. (1983)	$N = 10$ adult male students	Double-blind; approximately half the subjects were switched to decaffeinated coffee after 504 mg/day caffeine in coffee for 4 wks	Although tolerance developed to caffeine's effects on blood pressure, blood pressure was not affected by substitution of decaffeinated coffee
Edelstein et al. (1983)	$N < 430$ residents of a psychiatric hospital	Not blind; subjects consumed 3 or more caffeinated beverages/day; decaffeinated beverages were substituted for caffeinated beverages	Headache occurred during first 1–2 wks of decaffeinated beverages
Carter (1984)	$N = 32$	Double-blind; regular coffee drinkers (38 cups/week for 19 years); approximately half of the subjects were switched to decaffeinated coffee after five days of caffeinated coffee	No withdrawal symptoms occurred during actual period of decaffeinated coffee, although symptoms did appear during periods that subjects believed they were on decaffeinated coffee
Mathew and Wilson (1985)	$N = 16$ adult men and women	Not blind; heavy caffeine users (estimated 986 mg/day) and light caffeine users (estimated 126 mg/day) abstained from caffeine for 24 h	A bilateral increase in cerebral blood flow occurred in several frontal regions of the heavy caffeine user group only; although a "few" subjects reported withdrawal symptoms, no significant increase in headache occurred
Griffiths et al. (1986a)	$N = 7$ adult men; most with histories suggesting drug or alcohol abuse	Double-blind; heavy caffeine users were switched to decaffeinated coffee after consuming caffeinated coffee for an average of 10 consecutive days (mean of 1.25 g/day caffeine base during last 5 days)	Orderly syndrome developed with onset latency of 19 h, peaking on the 1st or 2nd day, then decreasing over the next 5–6 days; subjects reported more headache and being more sleepy, more lazy, less alert and less active; other withdrawal effects included changes in staff ratings of subject mood and behavior, decreased cigarette smoking, and trend in psychomotor performance impairment; 100% of subjects reported withdrawal headache

et al. 1980; Cobbs 1982; Weil and Rosen 1983 p 183; Rainey 1985; Griffiths et al. 1986a). For example, in one early report of caffeine withdrawal, Bridge (1893) noted that in susceptible individuals, "Headache often occurs during the first day or two in so severe a degree as to compel the individual to keep his bed..." An early experimental study by Dreisbach and Pfeiffer (1943) documented that "headache as extreme in severity as the subjects had ever

xperienced was produced by the sudden withdrawal of caffeine." This extreme headache occurred in 55% of 38 trials on 22 individuals comprising a relatively unselected subject opulation.

Time course. The caffeine withdrawal syndrome follows an orderly time course. Onset generally has been reported to ccur 12–24 h after terminating caffeine intake (Dreisbach nd Pfeiffer 1943; Goldstein 1964; Goldstein and Kaizer 969; Goldstein et al. 1969; Naismith et al. 1970; Greden et al. 1980; Mathew and Wilson 1985; Griffiths et al. 986a; Wilkin 1986), although two studies have described nset as early as 3 or 6 h (Roller 1981; Cobbs 1982). Fatigue has been described as preceding headache or cerebral fullness in some reports (Dreisbach and Pfeiffer 1943) but not n others (Roller 1981; Cobbs 1982). Intensity of caffeine ithdrawal has generally been described as peaking at 20–48 h of abstinence (Dreisbach and Pfeiffer 1943; Greden et al. 1980; Griffiths et al. 1986a; Wilkin 1986). The duration of caffeine withdrawal has most often been described o be about 1 week (Horst et al. 1934; Greden 1974; Mackenzie et al. 1981; Griffiths et al. 1986a), although substantial differences across individual subjects have been noted Griffiths et al. 1986a) and one clinician has suggested that protracted withdrawal signs or symptoms may occur for several months after terminating caffeine intake (Mendel 1889).

Pharmacological specificity. The pharmacological specificity of the physical dependence to caffeine has been established by a number of different observations. First, the severity of withdrawal appears to be an increasing function of the caffeine maintenance dose. Such dose dependence has been shown repeatedly in studies comparing groups of subjects that differ in self-selected histories of caffeine consumption Goldstein 1964; Goldstein and Kaizer 1969; Goldstein et al. 1969; Naismith et al. 1970; Winstead 1976; Greden et al. 1980; White et al. 1980; Mathew and Wilson 1985), although an absence of dose dependence has been occasionally described (Greden et al. 1978; Victor et al. 1981). It should also be noted, however, that dose dependence has not yet been demonstrated in a prospective experimental study. A second type of observation suggesting the pharmacological specificity of caffeine physical dependence is that withdrawal can be produced by caffeine administered in capsules (Dreisbach and Pfeiffer 1943) as well as by caffeine administered in beverages (cf. Tables 1 and 2). Third, caffeine ingested in capsules or tablets (Dreisbach and Pfeiffer 1943; Greden 1974), or in beverages (Kingdon 1833; Guelliot 1885a; Gilles de la Tourette and Gasne 1895; In Der Beeck 1961; Goldstein et al. 1969; Greden et al. 1980; Roller 1981; Cobbs 1982; Weil and Rosen 1983 p 183) can suppress symptoms of caffeine withdrawal induced by caffeine abstinence. Fourth, the magnitude of suppression by caffeine of symptoms induced by caffeine abstinence is an increasing function of caffeine dose (Goldstein et al. 1969). Fifth, caffeine is more effective in suppressing withdrawal headache than oxygen inhalation or administration of acetylsalicylic acid, benzedrine sulfate or amyl nitrite (Dreisbach and Pfeiffer 1943).

Proportion of population at risk and individual differences. From the available data, it is difficult to estimate what proportion of heavy caffeine consumers will experience symptoms after caffeine abstinence. There are four published experimental studies which provide information about the proportion of heavy caffeine using subjects (estimated ≥ 500 mg caffeine/day) experiencing caffeine withdrawal headache. In two studies, 100% of subjects reported headache (Griffiths et al. 1986a; Naismith et al. 1970). A considerably lower figure of 25% can be estimated from a study by Goldstein (1964) based on the total number of withdrawal trials conducted. This relatively low rate of withdrawal may be due to a relatively shorter period of withdrawal (approximately 18 h) which terminated with breakfast after a night of sleep. All three of these studies involved potentially biased subject groups that were specifically selected because of the subjects' high use of caffeine. The fourth study (Dreisbach and Pfeiffer 1943), in contrast, involved a relatively unbiased population of students with varied histories of caffeine use. During caffeine abstinence after a period of experimentally administered caffeine in capsules, 82% of the subjects experienced headache, with no clear influence of baseline rate of caffeine use (i.e. all three subjects who were previously caffeine abstainers experienced headache during withdrawal of experimentally administered caffeine).

The percentage of heavy caffeine users experiencing caffeine withdrawal headache in these experimental studies is high relative to that reported by heavy caffeine users in retrospective questionnaire surveys: 8% (Goldstein and Kaizer 1969), 11% (Greden et al. 1978), and $\leq 10\%$ (Winstead 1976). This discrepancy might be attributable to the possibility that heavy users infrequently omit daily caffeine and have little experience with withdrawal headache (Greden et al. 1978).

It should also be noted that, although caffeine withdrawal symptoms have been frequently reported in experimental studies, such symptoms are not an invariant consequence of termination of high dose consumption. There are instances in which individuals with histories of heavy caffeine use apparently experienced no symptoms upon abrupt termination or restriction of caffeine (Reimann 1967; Carter 1984). Also, as described previously, 12 reports of abrupt and/or gradual withdrawal from caffeine after chronic, high dose caffeine consumption were excluded from the tables because it was unclear whether caffeine withdrawal signs or symptoms were explicitly looked for or documented. It is possible that some or all of these reports represent instances in which withdrawal signs and symptoms were totally absent. It is important to recognize, however, that absence of symptoms does not necessarily indicate an absence of physical dependence. For example, Mathew and Wilson (1985) showed that caffeine abstinence produced reliable increases in cerebral blood flow but only inconsistent reports of withdrawal symptoms.

A more thorough understanding of individual differences will be important for determining what proportion of the general population is a risk for experiencing significant caffeine withdrawal effects. Animal and human studies have clearly documented substantial differences between individual subjects in the behavioral effects of caffeine (e.g. Goldstein et al. 1965b; Logan et al. 1986; Seale et al. 1986), including the reinforcing effects (Griffiths and Woodson 1987). Consistent with these observations, human caffeine withdrawal studies have documented substantial differences across subjects with respect to incidence (Dreisbach and Pfeiffer 1943) or continuance (Griffiths et al. 1986a) of

headache after abrupt caffeine withdrawal. The possibility should be explored that heavy coffee users are inherently more susceptible to the reinforcing and/or physical dependence producing effects of caffeine. Further research will also be necessary to establish the reliability of and mechanism(s) for these individual differences in caffeine reinforcement and physical dependence.

Minimum dosing parameters for caffeine withdrawal. Although there is relatively little information available on the minimum dosing parameters necessary for the expression of caffeine physical dependence, some evidence suggests that withdrawal phenomena may be detectable after relatively short-term exposure to high caffeine doses or after long-term exposure to relatively low doses. Two studies documented caffeine withdrawal headache upon abrupt termination of high doses of caffeine (terminal doses ≥ 600 mg/day) administered for 6–15 days. One of these studies was conducted with three subjects who were normally caffeine abstainers (Dreisbach and Pfeiffer 1943)

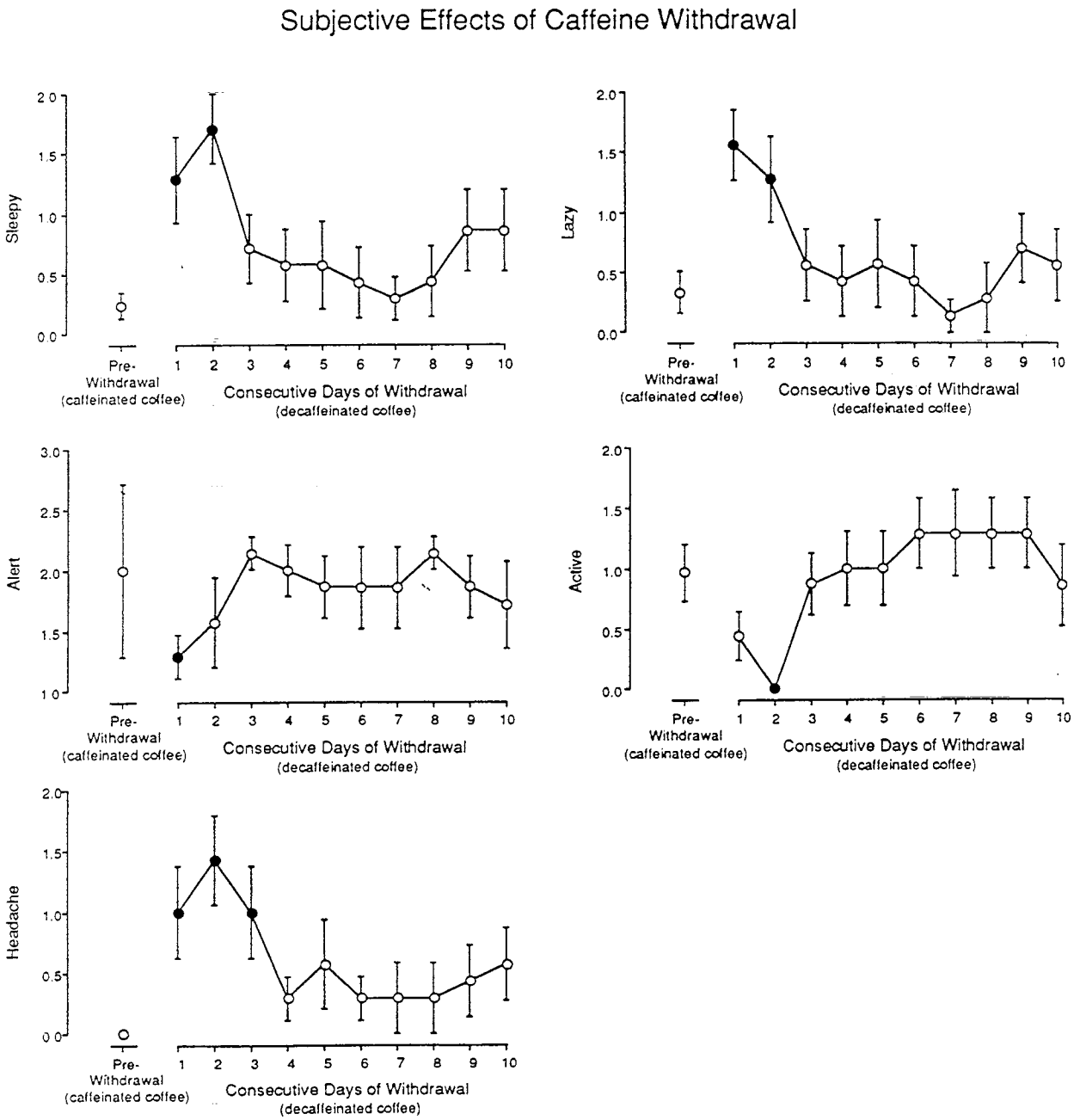

Fig. 1. Caffeine withdrawal: effects of substituting decaffeinated coffee for caffeinated coffee on subject-rated adjective clusters in seven subjects. The decaffeinated phase was preceded by a mean of 10 successive days of drinking only caffeinated coffee (100 mg caffeine per cup). *y-Axes*: 12:30 P.M. ratings on five adjective clusters. *x-Axes*: consecutive days; pre-withdrawal data show mean daily results from the 5 days which preceded substitution of decaffeinated coffee. Each data point with brackets indicates mean ± 1 SEM for seven subjects ($N=7$). *Filled data points* indicate which decaffeinated coffee days were significantly different ($P<0.05$) from the 5-day pre-withdrawal period. (Figure adapted from Griffiths et al. 1986a)

while the other study involved three subjects with histories of heavy caffeine use who were caffeine abstinent for 13–17 days (Griffiths et al. 1986a). The latter study also suggested that 11–15 days of high dose caffeine exposure may not be sufficient for producing the maximal degree of caffeine physical dependence as reflected in frequency of headache. A suggestion that withdrawal can occur after long-term exposure to relatively lower doses of caffeine has been provided in clinical descriptions (Schlesinger 1931) and in two studies which showed nonsignificant elevations in withdrawal symptoms after chronic, self-selected exposure to two to four cups of coffee/day (Goldstein 1964; Goldstein and Kaizer 1969). Given the large size of the population at risk, it will be important for future research to determine whether a clinically significant low dose caffeine withdrawal syndrome can be reliably detected.

Therapeutic detoxification from high doses of caffeine. In response to the toxic manifestations of caffeinism and associated health risk concerns, therapeutic detoxification from caffeine has been and is presently often suggested as a logical therapeutic strategy. Clinicians have made widely varying recommendations about the best procedures for accomplishing caffeine detoxification, including: (1) abrupt abstinence (Roch 1916); (2) gradual dose tapering (Guelliot 1885b; Bridge 1893; Greden 1981; Khoury and Maltbie 1984) sometimes in the context of structured behavior modification programs (Foxx and Rubinoff 1979; Bernard et al. 1981; James et al. 1985); and (3) pharmacological replacement with caffeine-containing medication (Rugh 1896; Stransky 1932; Dreisbach and Pfeiffer 1943; Greden 1981). A number of clinicians have also recommended the use of various other medications to provide symptomatic relief from the discomfort of caffeine withdrawal (Cole 1833; Guelliot 1885b, 1887; Bridge 1893; Dreisbach and Pfeiffer 1943; Greden 1981; Khoury and Maltbie 1984). The diversity of treatment strategies for caffeine detoxification probably reflects widely varying opinions and knowledge about the severity and frequency of a caffeine withdrawal syndrome. Given the documented wide individual differences in severity and duration of caffeine withdrawal (Dreisbach and Pfeiffer 1943; Griffiths et al. 1986a), perhaps the wisest approach to caffeine detoxification is to deal with each case individually. Because of ease of implementation, abrupt cessation in a supportive therapeutic context can be attempted initially. If significant withdrawal symptoms develop during abrupt abstinence, the more involved procedures of caffeine replacement therapy, supplemental medication (e.g. acetylsalicylic acid), or structured behavioral dose tapering programs should be used (cf Greden 1981 for thoughtful suggestions about practical implementation of caffeine detoxification procedures in the context of medical practice). With continued progress in the precise characterization of the caffeine withdrawal syndrome, future research should focus on the development of empirically based treatment regimens of optimal efficacy.

An illustrative example of caffeine withdrawal. A recent characterization of behavioral and subjective aspects of the caffeine withdrawal syndrome in humans was provided in an experiment in which seven subjects with histories of heavy coffee drinking were switched abruptly, under double-blind conditions, from caffeinated coffee to decaffeinated coffee for 10 or more days (Griffiths et al. 1986a).

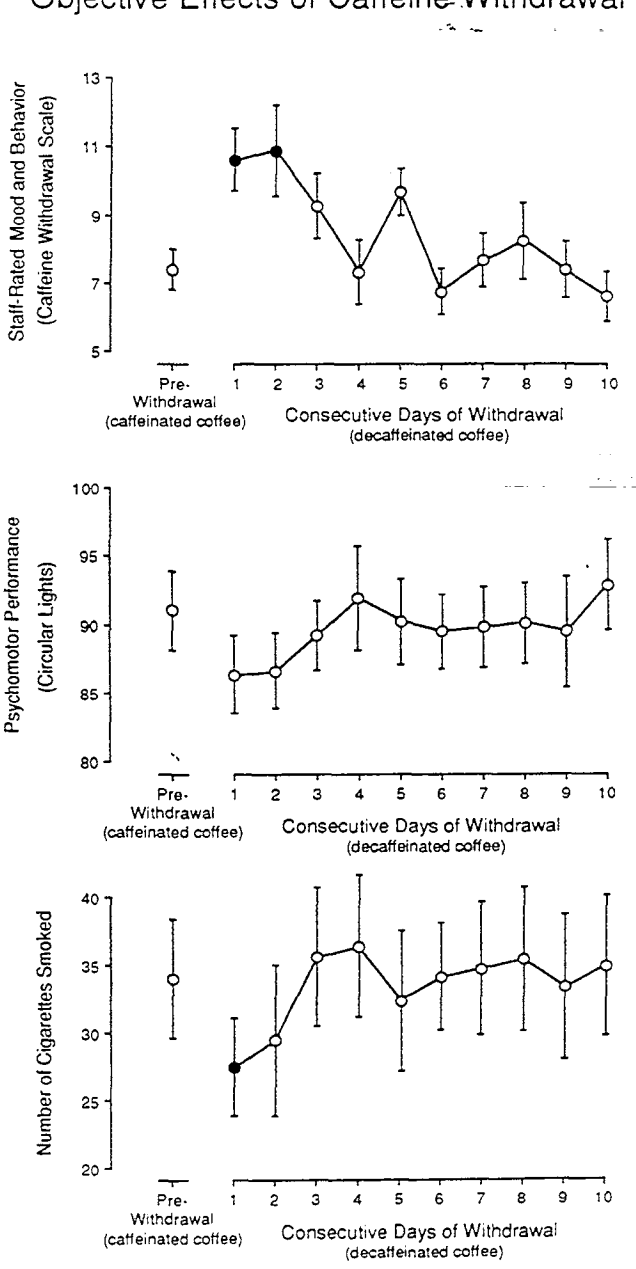

Fig. 2. Caffeine withdrawal: effects of substituting decaffeinated coffee for caffeinated coffee on objective measures of subject behavior. *y-Axes*: composite score from mean of 12:30 P.M. and 8:30 P.M. staff ratings of seven adjective clusters, psychomotor performance on a circular lights task, and number of cigarettes smoked. Other details are similar to those in legend of Fig. 1. (Figure adapted from Griffiths et al. 1986a)

Mean caffeine intake over the 5 days preceding the withdrawal phase was 1.25 g/day (range across subjects, 0.86–1.63 g/day). The withdrawal phase was the first occasion during their experimental participation (which averaged 19 days) that subjects were exposed to decaffeinated coffee for more than a 24 h period. As will be described in more detail in the following section, substitution of decaffeinated coffee did not significantly affect number of cups of coffee consumed but was associated with transient de-

creases in subject ratings of coffee liking. The results of the experiment also showed that substitution of decaffeinated coffee produced an orderly withdrawal syndrome which peaked on day 1 or 2 after substitution and then gradually subsided. Caffeine withdrawal produced significant increases in the Fatigue scale and significant decreases in the Vigor scale on the Profile of Mood States questionnaire, a standardized mood state inventory (McNair et al. 1971). Figure 1 shows significant effects of caffeine withdrawal on five subject-rated adjective clusters: 1) sleepy, tired, drowsy, half-awake; 2) lazy, sluggish; 3) alert, attentive, observant, able to concentrate; 4) active, stimulated, energetic; 5) headache. These were rated by the subjects on a 4-point scale (0 = definitely does not apply; and 3 = very strongly applies) on the basis of how they were feeling at the present time. In this study the most sensitive and reliable subject-rated withdrawal symptom was headache which occurred in all seven subjects and, for the group, remained significantly elevated over prewithdrawal levels through the 3rd day after substitution of decaffeinated coffee (Fig. 1).

Objective behavioral measures of caffeine withdrawal had the same time course as the subjective effects (Figs. 1 and 2). The top panel of Fig. 2 shows that changes in subject behavior were prominent enough to be detectable in ratings by observers who were blind to drug condition. For this measure, observers used a 4-point scale to rate the subject on seven adjective clusters (alert, content, active, sleepy, talkative, lazy, and irritable) on the basis of observing the subject over a 2-h period. The figure also shows that caffeine withdrawal was associated with a significant decrease in the number of cigarettes smoked as well as a trend toward disruption of psychomotor performance.

Physical dependence as a determinant of caffeine reinforcing effects in humans

A large number of experimental studies have evaluated various caffeine-induced subjective effects that might plausibly be related to the reinforcing properties of caffeine. This literature shows that, in contrast to amphetamine which generally produced elevations in ratings indicating "euphoria" and "well-being," caffeine did not consistently produce such effects (cf Weiss and Laties 1962; Chait and Griffiths 1983; Bättig 1985). A number of studies, in fact, showed that caffeine produced "dysphoric" changes in mood such as increases in anxiety and nervousness (e.g. Goldstein et al. 1965a; Greden 1974; Rapoport et al. 1981; Chait and Griffiths 1983; Charney et al. 1984).

Some of the clearest initial experimental evidence for positive mood changes produced by caffeine came from a survey and a clinical pharmacology study which showed that after overnight caffeine abstinence, heavy coffee users (≥ 5 cups per day) reported pleasant and desirable effects of coffee drinking and caffeine administration in contrast to coffee abstainers who reported unpleasant and undesirable effects (Goldstein and Kaizer 1969; Goldstein et al. 1969). The self-selected nature of the subject populations made it unclear whether the observed difference between heavy users and coffee abstainers was related to physical dependence or, alternatively, reflected some other pre-existing difference between these groups.

The reinforcing properties of caffeine in humans have been investigated more directly by adapting procedures originally developed in the animal drug self-administration laboratory (Griffiths et al. 1980). To date, five such human caffeine self-administration studies have been reported (Kozlowski 1976; Podboy and Malloy 1977; Griffiths et al. 1986a, b; Griffiths and Woodson 1987). These reports, which have been reviewed recently (Griffiths and Woodson 1987), show that under appropriate conditions caffeine can serve as a reinforcer.

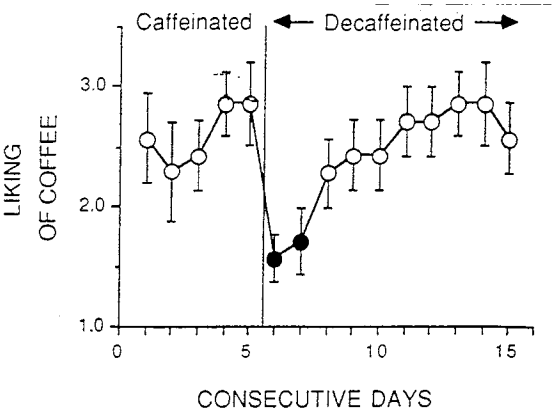

Fig. 3. Effects of substituting decaffeinated coffee for caffeinated coffee on subject rated coffee liking in seven subjects. The decaffeinated phase was preceded by a mean of 10 successive days of drinking only caffeinated coffee (100 mg caffeine per cup). *y-Axes*: 8:30 P.M. ratings of coffee liking. *x-Axes*: consecutive days. Each data point with brackets indicates mean ± 1 SEM for seven subjects ($N = 7$). *Filled data points* indicate which decaffeinated coffee days were significantly different ($P < 0.05$) from the 5-day period preceding substitution of decaffeinated coffee. (Figure adapted from Pharmacology Biochemistry & Behavior, R.R. Griffiths and P.P. Woodson, Reinforcing properties of caffeine: Studies in humans and laboratory animals, in press, Pergamon Journals, Ltd)

The results of one of these reports extend the observations by Goldstein (Goldstein and Kaizer 1969; Goldstein et al. 1969), discussed above, by providing the first experimental demonstration of the potentiation of the behavioral reinforcing effects of caffeine by physical dependence (Griffiths et al. 1986a). This report involved a series of experiments investigating the self-administration and reinforcing effects of caffeine in coffee in subjects with histories of heavy coffee drinking who resided on a research ward. One experiment, described in more detail in Section III, involved substitution of decaffeinated for caffeinated coffee under double-blind conditions. Although substitution of decaffeinated coffee did not significantly affect number of cups of coffee consumed, Fig. 3 shows that coffee liking decreased significantly on the first 2 days after substitution and subsequently progressively increased to pre-substitution levels. This transient decrease in liking was probably related to the caffeine withdrawal syndrome which was assessed concurrently on other subjective and objective measures and showed a similar time course (cf Section III and Figs. 1 and 2). To the extent that liking might predict reinforcing effects, these data provided suggestive evidence that, in subjects physically dependent on caffeine, decaffeinated coffee may be aversive relative to caffeinated coffee.

The implication that physical dependence may potentiate the relative reinforcing effects of caffeinated (100 mg per cup) versus decaffeinated coffee was investigated more directly in a subsequent experiment which utilized a double-

blind behavioral choice procedure (Griffiths et al. 1986a). On some days ("no choice" days), the available coffee was identified to subjects by a letter code. On "choice" days, two letter-coded coffees (to which the subject had previously been exposed) were available for consumption and subjects made a mutually exclusive choice as to which lettered coffee would be consumed that day. Subjects were exposed to these choice tests under two different "background" conditions (i.e. double-blind caffeinated or decaffeinated background condition in which subjects consumed only caffeinated or decaffeinated coffee for 1 week or more before the first choice test). The purpose of the background conditions was to determine whether a history of continuous caffeine exposure (i.e. induction of caffeine physical dependence) would increase the relative reinforcing effects of caffeinated versus decaffeinated coffee, as suggested by the liking data in Fig. 3.

The results showed that under the caffeinated background condition, caffeinated coffee was overwhelmingly preferred to decaffeinated coffee (92% of the occasions), while caffeinated coffee was not reliably chosen under the decaffeinated background condition (50% of the occasions). Subject ratings of liking from the no choice days were consistent with these behavioral choice results. Under the caffeinated background condition, caffeinated coffee was rated as better liked than the decaffeinated coffee, which was rated very unfavorably. Subjects complained that the decaffeinated coffee had low strength or low stimulant effect and several subjects attributed dysphoric symptoms (e.g. fatigue and headache which were probably due to caffeine withdrawal) to the decaffeinated coffee. Under the decaffeinated background condition, however, there was no such pronounced difference in liking between caffeinated and decaffeinated coffee. Subjects in this condition indicated that the decaffeinated coffee was satisfactory and they did not complain about the lack of strength or stimulant effect. Comparing across the two background conditions, it appeared that the difference in liking under the caffeinated background condition was due primarily to a decreased liking for the decaffeinated coffee rather than a change in liking for the caffeinated coffee. This result is consistent with the liking result shown in Fig. 3 and is probably attributable to caffeine withdrawal.

While these observations suggest that physical dependence (or at least a recent history of substantial caffeine intake) may substantially potentiate the reinforcing effects of caffeine, other data suggest that a history of substantial caffeine intake is not a *necessary* condition for caffeine to function as a reinforcer. In the choice study described above (Griffiths et al. 1986a) one of the subjects in the decaffeinated condition reliably chose caffeinated coffee over decaffeinated coffee. In another recent study (Griffiths and Woodson 1987), 12 normal healthy outpatient subjects were given opportunities to make a mutually exclusive choice between ingesting capsules containing 200 mg caffeine or placebo under blind conditions. Exposure and choice opportunities occurred under conditions in which subjects were required to be overnight abstinent from their normal dietary intake of caffeine. The results showed substantial differences across subjects with respect to the frequency of caffeine choice over ten independent choice trials. Interestingly, level of caffeine consumption prior to the study did not significantly correlate with per cent selection of caffeine ($r = 0.26$) and one of the four subjects who demonstrated significant choice preference for caffeine had a history of virtually no dietary intake of caffeine (estimated mean daily dietary caffeine intake prior to and during the study was about 3 mg). These isolated examples demonstrate that caffeine can function as a reinforcer in the absence of caffeine physical dependence.

To conclude this section, although not a necessary condition for caffeine to function as a reinforcer, several human studies suggest that physical dependence (or at least a recent history of substantial caffeine intake) may substantially potentiate the reinforcing effects of caffeine (Goldstein and Kaizer 1969; Goldstein et al. 1969; Griffiths et al. 1986a). These results are consistent with research in laboratory animals which has provided evidence for the reinforcing effects of caffeine in absence of a history of caffeine exposure (e.g. Deneau et al. 1969; Griffiths et al. 1979) and which has provided suggestive evidence for the aversive effects of caffeine abstinence in animals repeatedly exposed to caffeine (Vitiello and Woods 1977, Section II). It should be noted that the human research suggesting the importance of physical dependence to caffeine reinforcement has been conducted only in subjects with histories of very heavy caffeine use. It will be of interest to determine the extent to which physical dependence may be of significance in helping to establish and maintain the low-dose, chronic patterns of intake characteristic of normative caffeine use.

Mechanisms of caffeine physical dependence

The pharmacological and physiological mechanisms underlying caffeine physical dependence need considerable further elaboration. Accumulating evidence, however, suggests a role for the endogenous neuromodulator, adenosine. Caffeine is a competitive antagonist of adenosine (Snyder 1985) and chronic caffeine treatment has been reported to increase the number of brain adenosine receptors (Boulenger et al. 1983; Marangos et al. 1984; Chou et al. 1985; Ahlijanian and Takemori 1986), to shift brain A_1 adenosine receptors into a high affinity state (Green and Stiles 1986), and to increase functional sensitivity to adenosine (Von Borstel et al. 1983; Ahlijanian and Takemori 1986; Green and Stiles 1986). The increased functional tissue sensitivity to endogenous adenosine (e.g. in vascular and neural tissue of brain) has also been proposed as a mechanism for caffeine withdrawal headache and fatigue (Von Borstel et al. 1983; Hirsh 1984). Although an adenosine-related mechanism of caffeine physical dependence appears plausible, a carefully conducted recent study failed to demonstrate any enhanced sensitivity to the behavioral effects of R(−)-PIA (an adenosine agonist) under conditions in which tolerance to caffeine-induced stimulation of locomotor activity was present (Finn and Holtzman 1987; Holtzman and Finn 1987).

A role for the adrenergic mediation of some caffeine withdrawal effects is also suggested by recent studies. Operant behavioral experiments in rats which showed symmetrical cross-tolerance between caffeine and methylphenidate support previous behavioral studies suggesting noradrenergic mediation of caffeine effects (Holtzman 1987; Holtzman and Finn 1987). Repeated caffeine treatment has also been shown to decrease β-adrenergic receptor number (Goldberg et al. 1982; Green and Stiles 1986), while caffeine withdrawal was reported to decrease β-adrenergic receptor sensitivity (Mackenzie et al. 1981) and, in one patient, to increase ex-

cretion of the norepinephrine metabolite, MHPG (Gibson 1981).

As with the pharmacological mechanisms, the physiological mechanisms underlying caffeine withdrawal are incompletely understood. Several studies suggest that increased blood volume (possibly adenosine mediated) may be involved in caffeine withdrawal headache (Dreisbach and Pfeiffer 1943; Von Borstel et al. 1983; Hirsh 1984; Mathew and Wilson 1985). This research should be pursued and extended to determine whether other major withdrawal symptoms such as fatigue might also be mediated by caffeine withdrawal-induced hemodynamic effects. The possibility that the behavioral manifestations of caffeine withdrawal are epiphenomena of headache should also be explored. However, the observations that caffeine withdrawal-induced fatigue and/or mental confusion can occur in absence of headache (Kingdon 1833; Mendel 1889; Stransky 1932; In Der Beeck 1961; Greden 1974; Cobbs 1982) and that fatigue sometimes *precedes* headache as a withdrawal symptom (Dreisbach and Pfeiffer 1943) suggest that some caffeine withdrawal symptoms may be independent of headache.

Is caffeine a drug of abuse?

Historically caffeine has periodically been labeled as a drug of abuse (cf Guelliot 1885b; Gilbert 1976a; Austin 1979; Greden 1981), with analogies drawn to classic abused substances such as the opioids. This suggestion is controversial and almost invariably provokes rebuttals which include the observations that the great majority of caffeine use is consistent with socially accepted limits and patterns, that gross over-consumption of any article of diet can be harmful, and that the deleterious effects of excessive intake seem to be largely transient (Dews 1982). For socially domesticated psychoactive compounds such as caffeine, alcohol and nicotine, it is clear that instances of appropriate use as well as abuse can be identified and agreed upon, while this is not the case with illicit abused compounds. Thus it is understandable that analogies of caffeinism to opioid abuse can spark debate.

Perhaps a more useful approach to considering the relative abuse liability of caffeine is to consider the extent to which it has the defining characteristics of a drug of abuse. As discussed in more detail elsewhere (Griffiths et al. 1985), drugs of abuse have two major characteristics: (1) they have reinforcing properties and (2) they produce adverse effects (i.e. they have the capacity to harm the individual and/or society).

Physical dependence, the focus of this review, may contribute to the abuse liability of a drug in two ways: as a mechanism for enhancing the reinforcing properties and as an adverse effect. Although at times people appear to believe that the ability of a drug to produce physical dependence is the sine qua non of an abused drug, this has long been realized not to be the case and is constantly being rediscovered not to be the case (Kolb 1927; Isbell et al. 1948; Newman 1983). For instance, there are drugs that produce physical dependence without eliciting drug seeking behavior; there are drugs which are thought not to produce physical dependence but do produce substantial drug seeking behavior; and finally, there are situations in which the drug doses or schedules of drug availability preclude the development of physical dependence yet are associated with drug-seeking behavior (Griffiths et al. 1985).

With regard to the first characteristic of abused drugs (i.e. reinforcing properties), studies in humans and laboratory animals show that caffeine can serve as a reinforcer and can produce elevations in subjective drug liking or euphoria (Griffiths and Woodson 1987). Studies discussed in the present review also indicate that physical dependence can potentiate the reinforcing effects of caffeine. Although caffeine has reinforcing effects, caffeine can also be distinguished from classic drugs of abuse such as cocaine, *d*-amphetamine or pentobarbital which generally maintain high levels of self-administration (or liking) in contrast to caffeine which tends to maintain lower levels of self-administration (or liking) or maintain self-administration under a more narrow range of parametric conditions (Griffiths and Woodson 1987). Several types of clinical observations lend credence to these experimental studies of the reinforcing effects of caffeine. First, although wide individual differences probably exist, clinical reports have suggested substantial resistance of patients with chronic caffeinism to caffeine detoxification (Guelliot 1887; Bridge 1893; King 1903; Stransky 1932; Wagner 1939; Greden 1974; Furlong 1975; Stoffer 1979; Greden et al. 1980; Greden 1981; Wilkin 1986). Second, although few empirically verified studies have been conducted (James et al. 1987), experienced clinicians have estimated that relapse to caffeinism occurs in about two-thirds of treated patients (Greden 1980). Relapse to caffeine use appears to be especially likely when complete abstinence is the therapeutic goal (Kingdon 1833; Bridge 1893; Stransky 1932; Wagner 1939; Weil and Rosen 1983 p 183). Finally, clinical observations suggest that habitual patterns of analgesic use are more likely to develop with caffeine-containing analgesic preparations than with caffeine-free preparations (Collins and Turner 1973).

With regard to the second characteristic of abused drugs (i.e. adverse effects), a high prevalence rate for adverse effects associated with heavy caffeine use (caffeinism) has been suggested (10% for the adult population of North America) (Gilbert 1976b; Greden 1980). Importantly, however, research to date suggests that these effects are reversible. Caffeine withdrawal signs and symptoms represent the most clearly and extensively documented adverse effects of habitual caffeine use (this review). Ironically, while the extensive availability and use of caffeine-containing foods undoubtedly greatly increases the prevalence of caffeine physical dependence, the habitual social usage also reduces the likelihood that physically dependent individuals will actually experience caffeine abstinence and thus the adverse effects of withdrawal. In addition to the documented reversible adverse effects associated with caffeinism, the extent of additional significant health risk (e.g. heart disease or other non-reversible pathological consequences of chronic caffeine use) is controversial (Gilbert 1976a; Dews 1982; Ernster 1984).

The above analysis suggests that caffeine does indeed have the two defining features of prototypic drugs of abuse. Inasmuch as the relative abuse liability of a drug can be considered to be a multiplicative function of the degree of reinforcing properties and degree of adverse effects (Griffiths et al. 1985), the modest reinforcing properties and the modest adverse effects documented to date would suggest a low abuse potential relative to more widely recognized drugs of abuse. If future research reveals significant addi-

tional caffeine-associated health risk, however, the relative abuse liability of caffeine would be increased appreciably. In any event, a continued analysis of the interactive roles of the physical dependence producing and the reinforcing effects of the most widely used behaviorally active drug in the world should provide valuable insights into the general nature of the drug dependence process.

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